EVALUATION OF A NEW MEDICINE APPLICATION

Product Details	
Type of application:	Higher-risk medicine - Vaccine *This vaccine contains a new biological entity, so a data protection period will apply for 5 years from the date of gazette.*
Proposed trade name:	**COMIRNATY** COVID-19 mRNA vaccine (nucleoside modified)
Dose form:	Concentrated suspension for injection *Approved in the EU as 'concentrate for dispersion for injection'*
Drug substance and strength:	BNT162b2 [mRNA], 0.5 mg/mL (as 225 µg/0.45 mL) Each 0.3 mL dose of the diluted vaccine delivers 30 µg of RNA embedded in lipid nanoparticles. BNT162b2 [mRNA] is single-stranded, 5'-capped messenger RNA produced using a cell-free *in vitro* transcription from the corresponding DNA templates encoding the viral spike (S) protein of SARS-CoV-2. *The term 'tozinameran' has been proposed as an INN for the BNT162b2 drug substance and is currently under consideration by the World Health Organization (WHO).*
Classification:	Prescription
ATC code:	J07BX
Proposed indications and /or label claims	Comirnaty is indicated for active immunisation to prevent ~~against~~ coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2, in individuals ~~aged~~ 16 years of age and older ~~over~~. The use of this vaccine should be in accordance with official recommendations. *Indication wording revised to align with EU in roll 2.*
Administration & dosage:	*Administration:* Intramuscular injection. The multidose vial containing 0.45 mL of vaccine concentrate requires dilution with 1.8 mL 0.9% saline (not supplied with product) prior to use. Once diluted, the vial can deliver 6 doses ~~5 doses~~ of 0.3 mL. The multi-dose vial is preservative-free. *The number of doses that can be extracted from a single vial was updated by the company on 27/01/2021. The data*

	provided to support this change is discussed in the applicable sections of this report. *Dosage:* Adults and adolescents 16 years of age and older: Two doses of 0.3 mL given at least 21 days apart. Children under the age of 16: Safety and efficacy have not been established in children under 16 years of age.
Packaging & closure:	2 mL clear, glass (Type I) vial, closed with a bromobutyl rubber stopper, aluminium overseal and flip-off cap. The vials are enclosed in a cardboard carton.
Pack size:	195 multidose vials (1170 doses ~~975 doses~~) Each vial contains 0.45 mL of vaccine concentrate.
Storage conditions:	Unopened vials 6 months from the date of manufacture, stored in the freezer at -90°C to -60°C. Protect from light. Once removed from the freezer, the unopened vials can be stored for up to 5 days at 2 to 8°C, and up to 2 hours at temperatures up to 30°C, prior to use. Once thawed, the vaccine should not be refrozen. Diluted vials After dilution, the vials can be stored at 2 to 30°C for up to 6 hours. The data sheet notes that from a microbiological point of view (since there is no preservative), the product should be used immediately.
NZ sponsor:	Pfizer New Zealand Limited, Level 1, Suite 1.4, Building B, 8 Nugent Street, Grafton, AUCKLAND 1023
Manufacturers & packers:	Manufacture and testing of drug substance: Wyeth Biopharma Division of Wyeth Pharmaceuticals LLC, 1 Burtt Road, Andover, Massachussetts 01810, USA *Responsible for manufacture of drug substance, release and stability testing (composition, strength, identity, purity, process-related impurities, safety), and storage of cell banks.* BioNTech Manufacturing GmbH, An der Goldgrube 12, Mainz 55131, GERMANY *Responsible for manufacture of drug substance (in-vitro transcription, DNase I and Proteinase K digestion), release and stability testing (identity, purity, process-related impurities).* Rentschler Biopharma SE, Erwin-Rentschler-Strasse 21, Laupheim 88471, GERMANY *Responsible for manufacture of drug substance (ultrafiltration/diafiltration (UF/DF), dispensing), release and stability testing (composition, strength, safety).* BioNTech Innovative Manufacturing Services GmbH, Vollmersbachstrasse 66, Idar-Oberstein 55743, GERMANY

	Responsible for release and stability testing only (product-related impurities, purity). Not recorded on TPDR. Pfizer Inc, 875 Chesterfield Parkway West, Chesterfield, MO 63017-1732, USA *Responsible for release and stability testing of the drug substance (composition, strength, identity, purity, process-related impurities). The site also performs cell bank manufacture and storage, and manufacture and testing of the starting material (linear DNA template). Not recorded on TPDR.* <u>Manufacture, packaging and testing of drug product:</u> Pfizer Manufacturing Belgium NV, Rijksweg 12, Puurs B-2870, BELGIUM *Responsible for LNP fabrication and bulk drug product formulation, fill and finish, packaging (primary and secondary), release and stability testing (composition, adventitious agents), batch release by qualified person in European Economic Area (EEA)).* The NMA form also refers to i) Pharmacia & Upjohn Company LLC, 7000 Portage Road, Michigan, USA, for manufacture, testing (endotoxin and sterility) and packaging of the drug product, ii) BioNTech Manufacturing GmbH, An der Goldgrube 12, Mainz 55131, Germany for batch release of the drug product, and iii) Pfizer Pharma GmbH Betriebsstatte Karlsruhe, An der Tagweide 5, Karlsruhe 76139, Germany for drug product storage. These sites are not described in section 3.2.P.3.1. In direct discussions with the sponsor it was confirmed that these sites are not proposed for inclusion with the NMA. <u>Finished product testing:</u> Pfizer Ireland Pharmaceuticals, Grange Castle Business Park, Clondalkin, Dublin 22, IRELAND *Responsible for release and stability testing (identity, composition).* Wyeth Biopharma Division of Wyeth Pharmaceuticals LLC, 1 Burtt Road, Andover, Massachussetts 01810, USA *Responsible for release and stability testing (composition and strength, identity, potency, purity, adventitious agents).* Pfizer Inc, 875 Chesterfield Parkway West, Chesterfield, MO 63017-1732, USA *Responsible for release and stability testing (composition and strength, identity, potency, purity, adventitious agents).* Hospira Zagreb Ltd, Prudnicka cesta 60, Prigorje Brdovecko 10291, CROATIA *Responsible for release testing (sterility).* *Hospira is a wholly owned subsidiary of Pfizer Inc.* SGS Lab Simon SA, Vieux Chemin du Poete 10, Wavre B-1301, BELGIUM *Responsible for release testing (sterility).*

	The Hospira and SGS Lab Simon SA sites were not described in the NMA form but were confirmed to be relevant to the New Zealand application in pre-submission discussions with the sponsor. Both the Hospira and SGS Lab Simon sites have also been listed as sterility testing sites in section 3.2.P.3.1 of the CTD, and so have been considered as part of this application. BioNTech Manufacturing GmbH, Kupferbergterrasse 17-19, Mainz 55116, GERMANY *Responsible for batch release by Qualified Person in EEA. Not recorded on TPDR, as the New Zealand site of batch release performs this activity for product released to the New Zealand market.* New Zealand site of batch release: Pfizer New Zealand Limited, Level 1, Suite 1-4, Building B, 8 Nugent Street, Grafton, Auckland 1023
Overseas approvals:	Approved in the EU via the centralised procedure on 21/12/2020 and in Canada on 9/12/2020. The vaccine has also been granted authorisation for temporary/emergency supply in the UK and USA. The vaccine is currently under review in Australia, Switzerland and several other countries throughout the world.
Overseas evaluation reports provided:	None provided with the initial submission, but the EMA questions and final overview report were provided in subsequent data rolls.

CONTENTS

Administrative Data

Background

This new medicine application is for a new biological entity, hereafter referred to as BNT162b2[mRNA] (Pfizer code number PF-07302048) or by the trade name Comirnaty, which has been developed by Pfizer and BioNTech. The drug product is an RNA-based vaccine indicated for the active immunisation of individuals aged 16 years and over against COVID-19 disease caused by the SARS-CoV-2 virus.

The drug substance is a nucleoside-modified single-stranded, 5'-capped mRNA that encodes a prefusion stabilised full-length variant of the SARS-CoV-2 spike (S) glycoprotein. The spike protein is a surface protein on the virus that binds to angiotensin converting enzyme 2 (ACE-2) on host cells. It is considered a relevant antigen for vaccine development as antibodies against the spike protein have been shown to neutralise the virus and prevent infection. The mRNA is produced using cell-free *in vitro* transcription from a DNA template encoding the viral spike protein. The RNAs are encapsulated in lipid nanoparticles (LNPs), which protect the RNA from degradation by RNases and facilitate entry of the RNA into host cells. The mRNA is translated into the SARS-CoV-2 S protein in the host cell cytosol, and is then expressed on the cell surface where it induces an adaptive immune response.

The vaccine is formulated as a preservative-free concentrated suspension for injection, presented in a multi-dose vial. The product is supplied frozen (-90°C to -60°C), and must be thawed and diluted with sterile sodium chloride (0.9%) solution prior to administration by intramuscular injection.

The NMA is being filed as a rolling submission in three waves, based on data availability at the time of submission. Section 1.11.3 confirms that with the exception of Module 1, the New Zealand dossier is identical to that submitted in Australia, the EU, the USA, Canada, Switzerland and Singapore. The EMA questions (and company responses) were provided in the second and third submissions to Medsafe, and are acknowledged in this report where applicable. The CHMP issued a positive opinion granting conditional marketing authorisation for distribution of Comirnaty in the EU on 21 December 2020, and relevant aspects of the CHMP EPAR are referenced in this report.

The EU approval is conditional on the provision of additional characterisation data for the drug substance and drug product, and the continuation of the pivotal Phase 3 clinical trial. The specific obligations of the conditional EU marketing authorisation (taken from the public EPAR), are shown in Attachment 1 of this report. The Medsafe assessment concurs with these obligations, which are considered critical to support the quality, safety and efficacy of the drug product produced at commercial scale. The CHMP also made several recommendations for future quality development (refer Attachment 2). Since the New Zealand dossier aligns with that registered in the EU, the company will be asked to commit to provide Medsafe with the same additional information requested by the CHMP. Additional questions specific to the New Zealand application have also been identified as outlined in this report.

As discussed in the Quality Assessment Conclusion section of this report, Medsafe will seek expert advice from the Medicines Assessment Advisory Committee (MAAC) to determine what information is required prior to approval for distribution in New Zealand, and what can be accepted post-approval.

RFI1 Q.1.	***Please commit to provide Medsafe with the same additional information (specific obligations) requested by the CHMP as part of the conditional marketing authorisation in the EU, where applicable. The commitments made to the EMA and FDA to review the drug substance and drug product specifications as additional data becomes available, should also be made to Medsafe. The sponsor should note that Medsafe will seek expert advice from***

	the Medicines Assessment Advisory Committee (MAAC) to determine what additional information must be provided prior to approval for distribution of the vaccine in New Zealand, and what can be accepted post-approval.
EAI1 Q.1.	*The applicant has provided the commitments as requested, and acknowledged that Medsafe will seek expert advice from the MAAC. Although the company has given a commitment to provide Medsafe with the same additional information required by the EMA's specific obligations, the EMA also had a list of 'recommendations' for additional data, some of which should also be provided to Medsafe post approval. Conditions of the New Zealand provisional consent for this product will include the same specific obligations for quality data as required by the EMA/CHMP, along with some of the EMA/CHMP quality data 'recommendations'. The specific conditions will be included in the provisional consent are listed in the Final Recommendation section of this report, and are considered essential to ensure that NMA quality data requirements are fulfilled within a reasonable time frame.* ***Point resolved****.*

The sponsor has confirmed by way of the signed declaration in the NMA form that the product is not a hazardous substance or a new organism in terms of the HSNO legislation, and does not require EPA approval prior to being released in New Zealand.

Product name

The proposed proprietary name for the product is COMIRNATY (presented in capital letters on the labels and in the data sheet). This is the same name as registered for the vaccine in the EU and Australia; however, the EU SPC refers to the vaccine as 'Comirnaty' (ie in sentence case rather than capitalised). For ease of readability, the evaluator has used 'Comirnaty' in this report. There are no other products approved in New Zealand that start with the letters 'Comi'. The name is not misleading in any way with regards to the nature, purpose, uses or effects of the product. The proposed name is acceptable.

Labelling

In the original dossier submission, the company submitted full scale colour artworks of the vial and carton labels that refer to the trade name as Pfizer-BioNTech COVID-19 Vaccine. In roll 2, updated labels were provided with the proposed trade name Comirnaty. The company is unable to say whether the initial supply of vaccine in New Zealand will be in the updated or original labels, so both are being registered with this NMA.

On 27/01/2021, additional labels were provided that reference delivery of 6 doses rather than 5 doses. The information provided to Medsafe as of 27/01/2021 is that the vaccine supplied to New Zealand is likely to be packaged in the labels that reference delivery of 6 doses. The evaluator notes that the TGA approved both 5 dose and 6 dose labels, so both will be approved with this NMA to ensure uninterrupted vaccine supply to the New Zealand market.

The proposed labelling and packaging have been developed for global distribution. The company has stated that once supply and demand become manageable, region-specific labelling will be created and incorporated into the supply chain.

Vial label version 1 (Pfizer-BioNTech COVID-19 Vaccine)

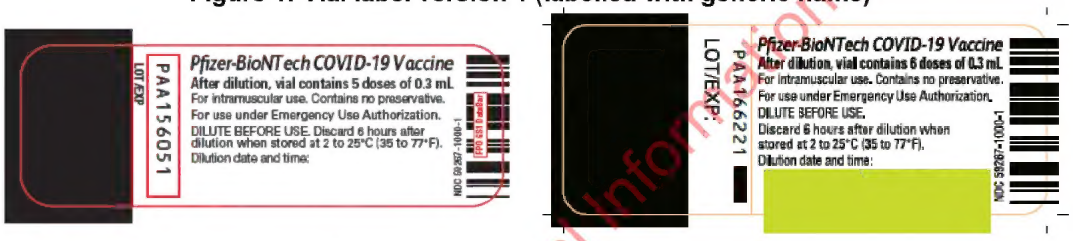
Since the proposed container is multidose, the vial label is subject to the full labelling requirements of regulation 13 of the New Zealand Medicines Regulations 1984. However, in alignment with the EU vaccine strategy, EMA/135540/2019 rev.4 *Recommendations for the implementation of the exemptions to the labelling and packaging leaflet obligations in the centralised procedure*, and EMA/616718/2020 *Questions and answers on labelling flexibilities for COVID-19 vaccines*, Medsafe will allow a labelling exemption to enable labelling and

packaging flexibilities for COVID-19 vaccines, to facilitate more rapid deployment of the product.

The information on the vial label proposed for initial global distribution of the vaccine (refer **Error! Not a valid bookmark self-reference.**) states the generic product name, batch number and expiry date, contents, and limited storage conditions. It does not mention the drug substance name or strength, but states that after dilution, the vial contains 5 doses of 0.3 mL. The absence of the statement of active substance has been allowed in principle by the EMA (pending suitable justification), as per EMA/616718/2020 (dated 27/11/2020). The label also includes a space for the vaccine administrator to write the date and time of dilution, and reminds the user to discard the product six hours after dilution. Although the vial (and carton) label refers to Emergency Use Authorization, which is not applicable in New Zealand, this is not considered a concern as it is clear this is a global medicine label (since it refers to storage conditions in °F), and distribution in New Zealand is contingent on Medsafe approval of the vaccine.

On 27/01/2021, an additional EU approved version of the label was provided that references delivery of 6 doses rather than 5 doses (right hand label).

Figure 1: Vial label version 1 (labelled with generic name)

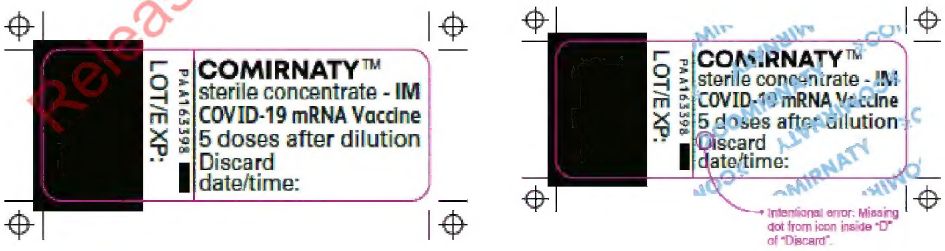


Vial label version 2 (Comirnaty)

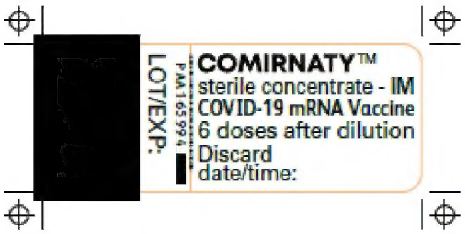
The vial labels with the proposed trade name are shown in **Error! Not a valid bookmark self-reference.**, with and without a varnish mock-up. There is even less information on the second version of the vial label; however, it still includes critical information such as the lot number, expiry date, and trade name. The evaluator notes that the first vial label has a space for writing the dilution date and time, whereas the second label has the discard date/time (ie 6 hours should be added to the dilution time). This difference has the potential to cause confusion so will need to be brought to the attention of vaccinators as part of a dear healthcare professional letter (DHPL). This is addressed in the below Request for Information (RFI).

Figure 2: Vial label version 2 (includes trade name Comirnaty)

5 doses



6 doses



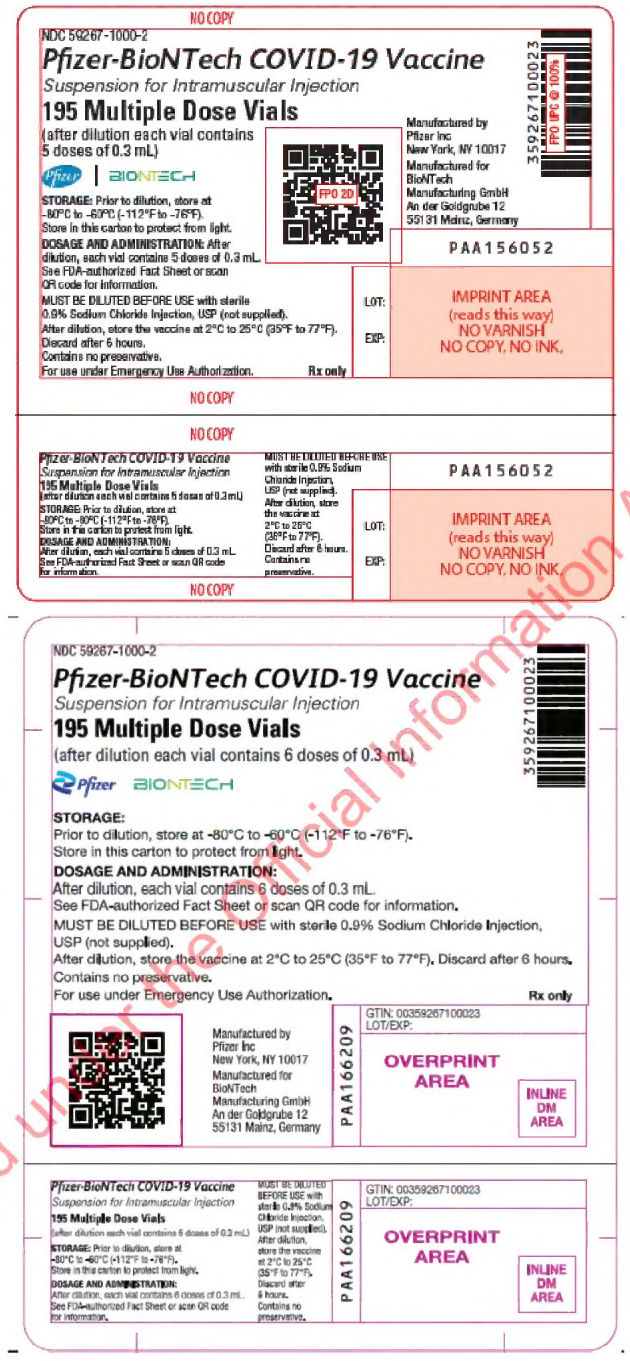
There is a note on the label artwork that the varnish is intentionally missing a dot from the icon inside 'D' of 'Discard'.

Carton label version 1 (Pfizer-BioNTech COVID-19 Vaccine)

The carton label with the generic product name proposed for initial global distribution of the vaccine is shown in Figure 3 and contains most of the information required by regulation 13 of the New Zealand Medicines Regulations 1984 for the labelling of medicines.

On 27/01/2021, an additional EU version of the label was provided (bottom label). A second version of the EU label was also provided that is identical to that shown in Figure 3 with the exception of the statement 'made in Germany' imprinted on it.

Figure 3: Carton label version 1 (labelled with generic name)



The following points are noted:

- the carton label does not state the name and strength/potency of the drug substance on either of the two panels
    - although this represents an area of non-compliance with New Zealand Medicines Regulations, the risk to patient safety as a consequence of the absence of this critical information is mitigated in part by the statement 'each vial contains 5 doses of 0.3 mL', which is repeated three times on the carton label
- the dose form description on the carton label is 'suspension for intramuscular injection' and does not mention that the product is a vaccine concentrate

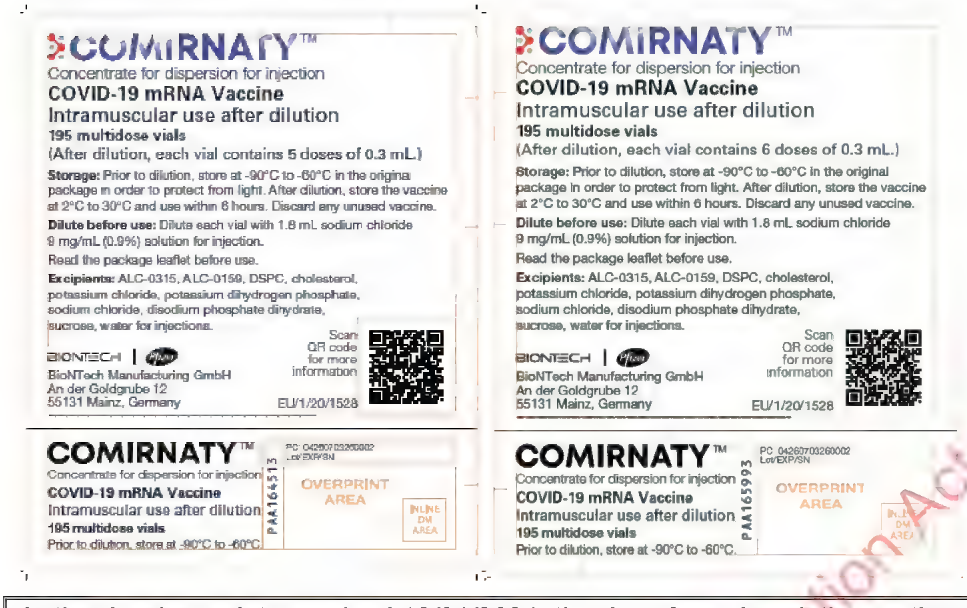
- this is not considered a significant safety concern, as the label clearly describes a requirement for dilution with 0.9% Sodium Chloride Injection, USP' (not supplied) before use

- the label includes the statement 'Rx only', which is recognised in New Zealand as meaning the product is a Prescription Only medicine
- the labels states the storage conditions for the unopened, undiluted product (-80 to -60°C, protect from light), and following dilution (2 to 25°C for up to 6 hours); the labels do not state the intermediary storage condition for the thawed but not yet diluted product (ie room temperature for no more than 2 hours, or in the refrigerator at 2 to 8°C for up to 5 days
- the Dosage and Administration information on the label directs the user to see the 'FDA-authorized Fact Sheet (the package insert) or to scan the QR code
    - The QR code links to the URL https://www.pfi.sr/pfebntcovidvax, which contains global information about the vaccine, with links to country specific information on administration. The company has been asked to confirm that New Zealand will be included in the list of countries after approval; refer RFI1 Q.2).

Carton label version 2 (Comirnaty)
The carton labels with the proposed trade name are shown in Figure 4, with and without a varnish mock-up.

Figure 4: Carton label version 2 (includes trade name Comirnaty)

Carton label version 2 (includes trade name Comirnaty) *cont.*



In the dossier update received 13/01/2021, the dose form description on the carton label was updated from 'concentrate for solution for injection' (top labels) to 'concentrate for dispersion for injection' (bottom labels).

On 27/01/2021, the label was updated to reference delivery of 6 doses (right hand bottom label) rather than 5 doses (remaining labels).

In email correspondence received 28/01/2021 the company confirmed that the carton labels received 13/01/2021 and 27/01/2021 are proposed to be used on the vaccine supplied to New Zealand. Any future changes to the labels will be submitted for Medsafe approval, as per normal regulatory requirements. The company also confirmed that the blue varnish 'COMIRNATY' on the labels is transparent and does not impact the legibility of the text on the labels. This is acceptable.

The updated carton labels with the Comirnaty trade name differ from the original labels with regards to the product name, dose form description ('concentrate for solution for injection' versus 'suspension for intramuscular injection'), and storage temperature ranges (unopened: -90°C to -60°C versus -80°C to -60°C; diluted: 2°C to 30°C versus 2°C to 25°C). Version 2 of the label no longer refers to emergency authorization and refers simply to dilution with sodium chloride rather than requiring USP saline. The QR code links to a splash page (https://www.pfi.sr/comirnatyglobal) that requires the user to select their country of origin to access information specific to their location. Currently, the splash page and listed countries appear specific to the EU approval of the vaccine (the QR code on the original label links to a more generic splash page that provides global information on the vaccine). The company will be asked to confirm that New Zealand will be added to the list of countries linked to from both QR codes following approval.

RFI1 Q.2. ***Please confirm that New Zealand will be included in the list of countries for region specific product information accessed via the QR codes on the proposed carton labels, and describe what information will be linked to from these webpages (eg the current approved New Zealand data sheet for Comirnaty). Since the information forms part of the registered product details for this vaccine, any changes to the content held at the URLs post-approval that is relevant to the product marketed in New Zealand should be***

communicated to Medsafe via the changed medicine notification (CMN) process.

EAI1 Q.2. *The applicant has explained that the QR codes connect to either the cvdvaccine.com or www.comirnatyglobal.com website. From there the individual accessing the website can select 'Health care professional' or 'Not a health care professional' and the specific country in which they are located, e.g. New Zealand. The applicant states that the website then directs to the locally approved label/data sheet. Although a data sheet is appropriate for health care professionals, the applicant has not explained what information a non-health care professional will be directed to.* ***This needs to be clarified as part of the outcome of evaluation but need not delay approval of this NMA.*** *The applicant has confirmed that Medsafe will be notified via CMN of any changes to the content on the URL that is relevant to product marketed in New Zealand.*

The following areas of non-compliance require a labelling exemption:

- the dose form is incorrectly described as a concentrate solution for injection, whereas is should be described as a concentrate suspension for injection (if the carton label supplied on 13.01.2021 is the label intended for the New Zealand market, then the description of the dose form as 'concentrate for dispersion for injection' is acceptable and does not require a labelling exemption)
- the carton labels do not include the name and strength of the active ingredient
- the absence of a classification statement
- the storage conditions are incomplete and do not include thawing conditions (time and temperature). Considering storage conditions are critical to the stability of this product, thawing conditions should also be included on the label

The evaluator also notes the statement in the fact sheet/package insert that 'some vials and cartons of Pfizer-BioNTech COVID-19 vaccine multiple dose vial may be labelled as BNT 162b2 (SARS-COV-2-mRNA vaccine) 5-dose vial'. Although these latter labels are not proposed for New Zealand, the fact they are referenced in a package insert that could be supplied in this country means that this should also be noted in a Dear Healthcare Professional Letter (DHPL) that accompanies release of this product to the New Zealand market. The company will be asked to provide a DHPL for review, that addresses the below points.

RFI1 Q.3. ***Since the first shipments of vaccine for the New Zealand market will be supplied in international labelling that does not comply fully with New Zealand medicines regulations, the company is asked to provide a 'Dear Healthcare Professional Letter' to accompany release of the product. Information included in the letter should address (but is not limited to) the following:***
i) The letter should identify the international labelling that will be used for distribution of the vaccine in New Zealand. The inclusion of colour photograph(s)/artwork(s) of the labels in the letter is encouraged. If both versions of the labels will be used, differences between the labels should be identified. For example, on one set of labels the administrator is informed to write the dilution date/time, whereas the other label set requires the administrator to write the discard date/time.
ii) Depending on what version of the labels will be used, the company should clarify that the statement 'For use under Emergency Use Authorization' on the US labels is not relevant to New Zealand, that the sodium chloride used for dilution can be Ph. Eur. quality (not just USP quality), and to explain reference to labelling of some vials as 'BNT 162b2 (SARS-COV-2-mRNA vaccine) 5-dose vial' (as mentioned in the fact sheet/package insert) is not

	relevant to New Zealand. ***iii) Clear storage conditions should be provided on the letter, including storage conditions for frozen, thawed/unopened product and diluted product. This is of particular importance, as the intermediary storage condition (ie for the thawed but not yet diluted product), is not listed on the label.*** ***Please provide (or commit to do so prior to launch of the vaccine to the New Zealand market), a draft DHPL that addresses the above concerns.***
EAI1 Q.3.	*The applicant has indicated that a 'Dear Healthcare Professional' letter is being prepared and will be provided to Medsafe prior to launch of this vaccine. The company will be informed that the letter should also address the requirement for the use of low dead-volume syringes and needles in order to extract 6 doses from a single vial (this change was introduced on 27/01/2021). The DHPL should also reiterate that if the amount of vaccine remaining in the vial after the fifth dose cannot provide a full dose (0.3 mL), the healthcare professional must discard the vial and its contents. There should be no pooling from multiple vials to make up a full dose, and any unused vaccine should be discarded 6 hours after dilution.* ***It is critical that Medsafe receives and reviews this letter prior to marketing of this vaccine. The provisional consent for this product will include the requirement to prepare a Dear Healthcare Professional letter and provide this to Medsafe for review and approval prior to distribution of this product.***

Labelling exemption

On the basis that i) the proposed vaccine has been developed in response to the current global COVID-19 pandemic, and ii) will be supported by a comprehensive information programme for New Zealand healthcare professionals, the company's request for a labelling exemption for the noted areas of non-compliance will be granted. The labelling exemption for the two sets of international vial and carton labels will be valid for the duration of the s23 approval granted at gazettal of this NMA, or until approval of New Zealand specific labelling, whichever occurs first.

Data sheet and package insert

A draft New Zealand data sheet was provided with roll 2. Medsafe's assessment of the clinical information in the data sheet is documented in a separate report.

The data sheet mostly complies with New Zealand medicines regulations requirements. The following points were noted from assessment of the roll 2 information:

i) The data sheet refers to the product as Comirnaty, BNT162b2, COVID-19 vaccine. Consistent reference to the trade name 'Comirnaty' is required.

ii) *Section 1*: It is considered incorrect to refer to the strength as 30 µg/0.3 mL next to 'concentrated suspension for injection' as this is the strength of the diluted vaccine (ie the strength of the undiluted vaccine is 0.5 mg/mL).

iii) *Section 2*: The statement 'One vial contains 5 doses of 30 micrograms (0.45 mL of BNT162b2 [mRNA]) embedded in lipid nanoparticles' is considered confusing, and should be revised to state 'One vial (0.45 mL) contains 5 doses of 0.3 mL after dilution. One dose (0.3 mL) contains 30 micrograms of COVID-19 mRNA vaccine embedded in lipid nanoparticles'

iv) *Section 4.2*: For clarity, a separate heading for 'Elderly population' should be added, with the statement 'No dosage adjustment is required in elderly individuals ≥ 65 years of age'.

v) *Section 5.1*: The ATC code J07BX should be added as per the EU SPC.

vi) *Section 6.3*: For clarity, information in this section should include both the unopened vial and the diluted medicinal product, as per the EU SPC for Comirnaty.

In roll 3, received 8/01/2021, an updated data sheet was provided that addressed the points raised in i), iii), iv), v) and vi). One additional change is still required as detailed below. As part of the data sheet update, the company revised the storage and handling information to align with the EU SPC for Comirnaty (includes pictorials as part of the instructions). This is acceptable.

RFI1 Q.4. ***Please make the following change to the proposed data sheet:***
i) Section 1: Please change the strength description of the vaccine concentrate to 0.5 mg/mL, as 30 µg/0.3 mL is the strength of the diluted vaccine.

EAI1 Q.4. The data sheet has been updated as requested. The data sheet has also been updated to include the following:

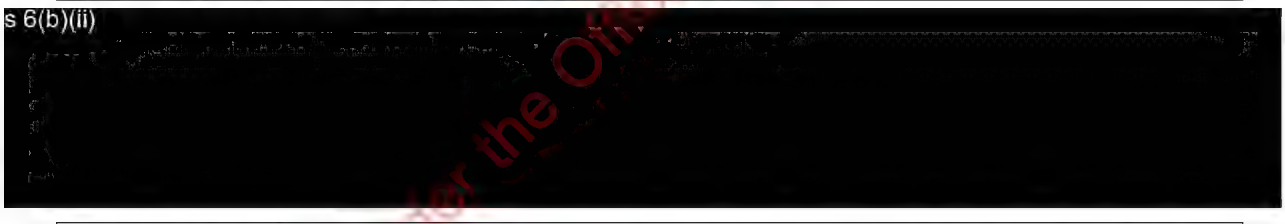
- an additional statement regarding use in children and adolescents less than 16 years of age, i.e. "Limited data are available in this age group".

- a traceability statement in section 4.4. 'Special warnings and precautions for use', "In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded". The applicant states that the statement was included at the request of the TGA. Although the New Zealand data sheet is published separately to the TGA approved Product Information, inclusion of this statement is acceptable.

-editorial change to the statement in section 4.4. regarding close observation is recommended following vaccination.

The proposed changes are acceptable. ***Point resolved****.*

s 6(b)(ii)



On 27/01/2021, Medsafe received a request from the company to revise the number of doses that can be delivered from a single vial from 5 doses to 6 doses. The information provided in support of the delivery of 6 doses is discussed in section 3.2.P.2.2 of this report. The proposed change has been approved by both the EMA and the TGA. Applicable sections of the data sheet and CMI have been updated to reference the 6 doses. Notably, the revised data sheet (and current EU approved SPC for Comirnaty) describe a requirement for the use of low dead-volume syringes and/or needles (no more than 35 µL dead volume) to extract 6 doses from a single vial. If standard syringes and needles are used, there may not be sufficient volume to extract a sixth dose from the vial. The data sheet instructs the user to discard the vial if the amount of vaccine remaining in the vial cannot provide a full dose of 0.3 mL. ***A requirement for the use of low dead-volume syringes and needles in order to extract 6 doses from a single vial should be noted in the DHPL that will accompany release of the vaccine to the New Zealand market. The DHPL should also reiterate that if the amount of vaccine remaining in the vial after the fifth dose cannot provide a full dose (0.3 mL), the healthcare professional must discard the vial and its contents. There should be no pooling from multiple vials to make up a full dose, and any unused vaccine should be discarded 6 hours after dilution.***

The international medicine pack with the generic product name ('version 1') will be supplied with a fact sheet that details how the vaccine should be used. Although referred to as a

global document, the fact sheet is targeted towards the US market, as it refers to the US FDA Emergency Use Authorization (EUA) of the unapproved product, and the FDA mandatory requirements for use under the EUA. The document directs the user to www.cvdvaccine.com for the most recent version of the fact sheet. This is the same webpage as the one linked to from the QR code on the label.

With the exception of the indicated age range (the fact sheet refers to use in individuals 18 years of age and older, whereas the company is seeking approval to administer to individuals in New Zealand aged 16 years and over), the dosage and administration information (presented graphically and with text descriptions) aligns with the details proposed in this NMA. The fact sheet notes that there are no data available on the interchangeability of the Pfizer-BioNTech COVID-19 vaccine with other COVID-19 vaccines to complete the vaccination series (two doses). The quality details in the fact sheet (formulation, storage, in use shelf-life) align with the product details proposed for registration in New Zealand.

Consumer medicines information (CMI) was provided in roll 2 and roll 3, and updated on 27/01/2021 to reflect the delivery of 6 doses rather than 5 doses. The information in the CMI aligns with that in the data sheet. The sponsor has signed the CMI commitment in the NMA form that following consent to distribute, an electronic copy of the CMI will be submitted to Medsafe and will comply with the requirements published on the Medsafe website.

GMP status of manufacturers and packers

The applicant has provided the following evidence of GMP compliance for the drug substance and drug product manufacturing, testing and packaging sites.

Table 1: Proposed manufacturing sites and GMP status

Manufacturing step	Site address	Authority	Certificate number	Expires
Drug substance manufacture and testing	BioNTech Manufacturing GmbH, An der Goldgrube 12, Mainz 55131, GERMANY	TGA	MI-2020-CL-10905-1 Authorises the site for active material manufacture of BNT162b2 (mRNA) and testing (sterility)	**9/01/2024**
	Rentschler Biopharma SE, Erwin-Rentschler-Strasse 21, Laupheim 88471, GERMANY	TGA	MI-2020-CL-10912-1 Authorises the site for active material manufacture of BNT162b2 (mRNA) and testing (biological, chemical and physical, endotoxin), packaging and storage	**31/03/2021**
	Wyeth Biopharma, Division of Wyeth Pharmaceuticals LLC, 1 Burtt Road, Andover, Massachussetts 01810, USA	TGA	MI-2020-CL-11475-1 Authorises the site for active material manufacture of BNT162b2 drug substance and COVID-19 vaccine endotoxin testing	**18/07/2022**

	Pfizer Inc, 875 Chesterfield Parkway West, Chesterfield, MO 63017-1732, USA	TGA	MI-2020-CL-10943-1 Authorises the site for testing (analytical, biological, chemical and physical, endotoxin) of sterile dosage forms and API (not defined)	**20/02/2022**
	BioNTech Innovative Manufacturing Services GmbH, Vollmersbachstrasse 66, Idar-Oberstein 55743, GERMANY	TGA	MI-2020-CL-10909-1 Authorises the site for testing (sterility, chemical and physical, biological, microbial) and irradiation of BNT162b2 mRNA	**30/04/2023**
	Pfizer Manufacturing Belgium NV, Rijksweg 12, Puurs B-2870, BELGIUM	TGA	MI-2020-CL-04395-1 Authorises the site for sterile finished product manufacture of injections, and testing (sterility, biological, endotoxins)	**31/12/2021**
Drug product manufacture, packaging and testing	s 9(2)(b)(ii) [redacted]			
	Pfizer Ireland Pharmaceuticals, Grange Castle Business Park, Clondalkin, Dublin 22, IRELAND	TGA	MI-2017-CL-00823-1 Authorises the site for sterile finished product manufacture and testing (microbial, biological, chemical and physical)	**9/05/2022**
Finished product testing only	Wyeth Biopharma, Division of Wyeth Pharmaceuticals LLC, 1 Burtt Road, Andover, Massachussetts 01810, USA	TGA	MI-2020-CL-02177-1 Authorises the site for testing (chemical and physical, biological, microbial, sterility)	**18/07/2022**
	Pfizer Inc, 875 Chesterfield Parkway West, Chesterfield, MO 63017-1732, USA	TGA	MI-2020-CL-10943-1 Authorises the site for testing (biological, chemical and physical, analytical, endotoxin) of sterile dosage forms and API (not defined)	**20/02/2022**

	Hospira Zagreb Ltd, Prudnicka cesta 60, Prigorje Brdovecko 10291, CROATIA	TGA	MI-2017-CL-13674-1 Authorises the site for sterile finished product manufacture, secondary packaging and testing (sterility, biological)	**22/09/2022**
	SGS Lab Simon SA, Vieux Chemin du Poete 10, Wavre B-1301, BELGIUM	TGA	MI-2017-CL-03231-1 Authorises the site for testing (chemical and physical, sterility, biological and microbial)	**31/12/2021**

The drug product manufacturing sites Pharmacia & Upjohn Company LLC, BioNTech Manufacturing GmbH and Pfizer Pharma GmbH are not proposed for the initial registration of the product in New Zealand.

The GMP evidence is acceptable. **The company will be reminded as part of the outcome of evaluation email to provide updated evidence of cGMP for Rentschler Biopharma SE, Erwin-Rentschler-Strasse 21, Laupheim 88471, Germany, when available, as the current clearance will expire on 31/03/2021.**

Module 3.2.S. Drug Substance

Background

Several drug substance variants were investigated in the Pfizer/BioNTech non-clinical and Phase 1 COVID-19 vaccine clinical studies (refer below table).

Table 2: Drug substance candidates used in non-clinical and Phase I clinical studies

BNT162 vaccine candidate	RNA platform	Encoded antigen
s 9(2)(b)(ii)		
BNT162b2	Nucleoside Modified mRNA	Full length SARS-CoV-2 spike protein bearing mutations preserving neutralisation-sensitive sites
s 9(2)(b)(ii)		

On the basis of available safety and immunogenicity data (recipients demonstrated a favourable breadth of epitopes specific to the spike antigen, and concurrent induction of high magnitude CD4+ and CD8+ T cell responses against the receptor binding domain (RBD)), the variant BNT162b2 [mRNA] was selected to progress through to Phase 2/3 of the pivotal clinical study (C4591001).

The manufacture, characterisation and quality control of BNT162b2 [mRNA], is assessed in this report. At times reference is also made to the available data for BNT162b1, as supportive evidence.

3.2.S.1 General information

The drug substance, BNT162b2, is a single-stranded messenger RNA (mRNA), encoding a full-length, codon-optimised, pre-fusion stabilised conformation variant (K986P and V987P) of the SARS-CoV-2 spike (S) glycoprotein (the antigen).

3.2.S.1.1 Nomenclature

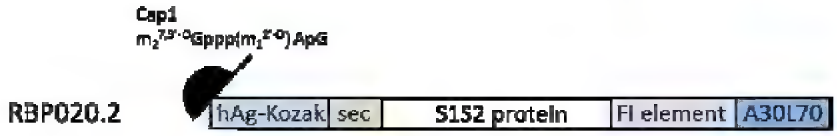
Table 3: Nomenclature of BNT162b2 drug substance

Product code:	BNT162b2
Laboratory code:	RBP020.2; ($m_2^{7,3'-O}$Gppp($m_1^{2'-O}$)ApG)-hAg-Kozak-S1S2-PP-FI-A30L70
Chemical class:	Ribonucleic Acid (RNA)
Encoded antigen:	Viral spike protein (S1S2 protein) of the SARS-CoV-2 (S1S2 full-length protein, containing two mutations: K986P and V978P)
CAS Registry Number:	2417899-77-3
CA Index Name:	RNA (recombinant 5'-[1,2-[(3'-O-methyl)m7G-(5'->5')-ppp-Am]]-capped all uridine->N1-methylpseudouridine-substituted severe acute respiratory syndrome coronavirus 2 secretory signal peptide contg. spike glycoprotein S1S2-specifying plus 5'- and 3-untranslated flanking region-contg. poly(A)-tailed messenger BNT162b2), inner salt
INN	Tozinameran (proposed INN)

3.2.S.1.2 Structure

A schematic illustration of the general structure of the BNT162b2 [mRNA] drug substance is shown below (not drawn to scale with regards to sequence lengths).

Figure 5: General structure of BNT162b2 [mRNA]



The structure is determined by the respective nucleotide sequence of the DNA used as the template for *in vitro* RNA transcription.

RNA sequence

The full sequence of BNT162b2 is shown in Attachment 3, and is based on the sequence of the 'Severe acute respiratory syndrome coronavirus 2 isolate Wuhan-Hu-1' (GenBank entries: MN908947.3 (complete genome), QHD43416.1 (spike surface glycoprotein)). The sequence length is 4284, which includes G to denote the presence of the 5'-cap analog (G: 1062, C: 1315, A: 1106, Y: 801). The company will be asked to comment on the RNA sequence in context of the B.1.1.7 (VOC-202012/01) and B.1.351 (501Y.V2) variant strains of SARS-CoV-2.

s 9(2)(b)(ii)

s 9(2)(b)(ii)

In addition to the codon-optimised sequence encoding the antigen, the RNA contains structural elements for mediating RNA stability and translational efficiency (5'-cap, 5'-UTR (hAg-Kozak), 3'-UTR (FI element), 3' poly(A)-tail (A30L70)). Furthermore, an intrinsic signal peptide (sec) is part of the open reading frame and is translated as an N-terminal peptide. Selection of the sequence elements was guided by the company's experience working with RNA transcripts, and the scientific literature (references provided). Key details of each of these elements are summarised as follows:

hAg-Kozak (nucleotides 2 to 54): 5'-UTR sequence of the human alpha-globin mRNA with an optimised 'Kozak sequence' to increase translational efficiency.

Sec (nucleotides 55 to 102): Corresponds to the intrinsic S1S2 protein signal peptide (sec), which guides translocation of the nascent polypeptide chain into the endoplasmic reticulum.

S1S2 protein (nucleotides 103 to 3879): Codon-optimised sequence encoding the spike antigen of SARS-CoV-2. The S1S2 protein or spike glycoprotein is expressed on membranes and facilitates recognition by the host cells, as well as cellular uptake. The protein sequence contains two proline mutations (K986P and V987P), which ensure an antigenically optimal pre-fusion confirmation (P2 S).

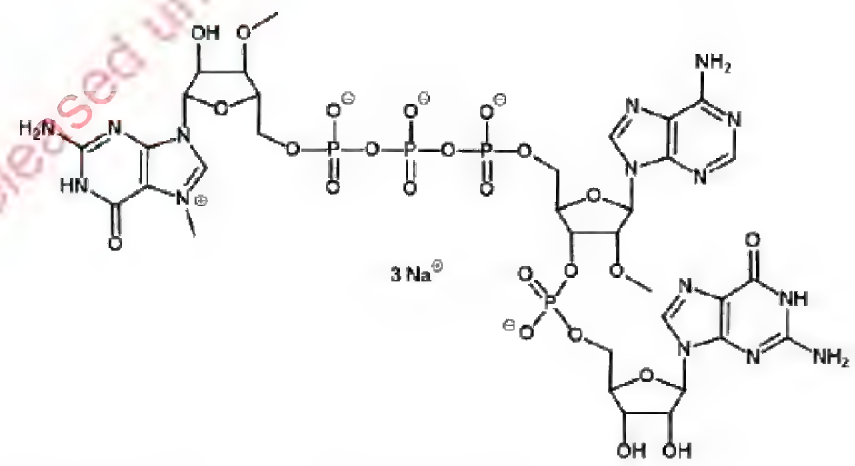
FI element (nucleotides 3880 to 4174): The 3'-UTR is a combination of two sequence elements derived from the amino terminal enhancer of split (AES) mRNA (called 'F') and the mitochondrial encoded 12S ribosomal RNA (called 'I'). These were identified by an *ex vivo* selection process for sequences that confer RNA stability and augment total protein expression.

A30L70 (nucleotides 4175 to 4284): A poly(A)-tail measuring 110 nucleotides in length, consisting of a stretch of 30 adenosine residues, followed by a 10 nucleotide linker sequence and another 70 adenosine residues. The poly(A)-tail is designed to enhance RNA stability and translational efficiency in dendritic cells.

mRNA cap

The 5' cap protects the drug substance from exonucleolytic activity and promotes translation of the protein antigen *in vivo*. The structure of the 5' mRNA cap (cap1) is shown below.

Figure 6: 5'-cap analog ($m_2^{7,3'\text{-}O}$Gppp($m_1^{2'\text{-}O}$)ApG)



The cap1 structure (containing a 2'-O-methyl group on the penultimate nucleoside of the 5'-end of the RNA chain) is incorporated into the BNT162b2 drug substance during *in vitro* transcription. For RNAs with modified uridine nucleotides, the cap1 structure is superior to other cap structures because cap1 is not recognised by cellular factors such as IFIT1.

Consequently, cap1-dependent translation is not inhibited by competition with eukaryotic translation initiation factor 4E. In the context of IFIT1 expression, mRNAs with a cap1 structure give higher protein expression (based on the available literature and manufacturing experience).

Use of the cap1 structure also leads to low amounts of uncapped transcripts. In general, the T7 polymerase prefers a guanosine as the priming nucleoside, leading to higher transcription efficiencies as compared to other starting nucleosides. Capping structures with a guanosine moiety compete with GTP for incorporation in the mRNA resulting in uncapped transcripts. The $m_2^{7,3'\text{-O}}$Gppp($m_1^{2'\text{-O}}$)ApG cap analog rescues transcription efficiency from templates starting with adenosines, because the ApG moiety of cap1 allows transcription initiation at the second position, a guanosine, thereby giving mainly capped mRNAs.

Modified uridine

The RNA does not contain any uridines. During synthesis of the RNA, the modified N1-methylpseudouridine triphosphate ($^{m1}\Psi$TP) is used in place of uridine triphosphate (UTP). This substitution has been made to enhance translation of the *in vitro* transcribed mRNA sequences by reducing its immunogenicity.

3.2.S.1.3 General properties

The BNT162b2 drug substance is formulated at a target concentration of 2.25 mg/mL in drug substance formulation buffer (10 mM HEPES, 0.1 mM EDTA, pH 7.0). The general properties of the drug substance are shown below.

Table 4: BNT162b2 drug substance general properties

Appearance	Clear to slightly opalescent, colorless to slightly brown liquid
Specific Absorption Coefficient (260 nm)	25 L/g × cm
Theoretical length[a]	4,283 nucleotides
Theoretical mass[b]	1,388,651 g/mol
pH	Target 7.0

a. Theoretical value has been verified by gel electrophoresis compared to a size marker. The length is 4,284 nucleotides when the presence of the 5'-cap analog (G) is included.
b. Theoretical value has been verified indirectly by control of RNA lengths.

The structural and functional studies conducted to characterise BNT162b2 are discussed later in this report.

3.2.S.2 Manufacture

3.2.S.2.1 Manufacturers

The following table summarises the responsibilities of the sites involved in the production of the BNT162b2 drug substance. Although three drug substance manufacturing sites are proposed, the Rentschler and BioNTech, Mainz (BNT Mainz) sites each perform different steps in the manufacturing process, contributing to the production of a single batch of drug substance.

Table 5: Manufacture and testing sites associated with the production of BNT162b2

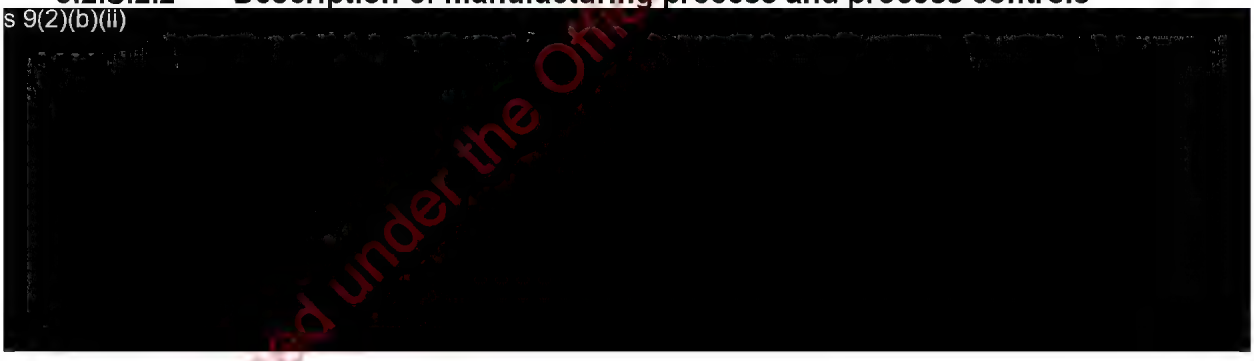
Site	Responsibility
Wyeth BioPharma Division of Wyeth Pharmaceuticals, LLC[a] 1 Burtt Road Andover, MA 01810 United States	Manufacture of drug substance Release and Stability Testing (Composition, Strength, Identity, Purity, Process Related Impurities, Safety)
Pfizer Inc 875 Chesterfield Parkway West Chesterfield, MO 63017 United States	Release and Stability Testing (Composition, Strength, Identity, Purity, Process Related Impurities)
BioNTech Manufacturing GmbH An der Goldgrube 12 55131 Mainz Germany	Manufacture of drug substance (In-vitro Transcription, DNase I and Proteinase K digestion) Release and Stability Testing (Identity, Purity, Process Related Impurities)
Rentschler Biopharma SE Erwin-Rentschler-Str. 21 88471 Laupheim Germany	Manufacture of drug substance (Ultrafiltration/Diafiltration (UFDF), DS Dispensing) Release and Stability Testing (Composition, Strength, Safety)
BioNTech Innovative Manufacturing Services GmbH Vollmersbachstraße 66 55743 Idar-Oberstein Germany	Release and Stability Testing (Product Related Impurities, Purity)

a. The legal entity name change from Wyeth BioPharma Division of Wyeth Pharmaceuticals was changed at the acquisition by Pfizer in 2009, since then the Wyeth Pharmaceuticals manufacturing site in Andover, Massachusetts belongs to Pfizer's production sites and is embedded in Pfizer's GMP system. Pfizer will be utilized throughout the CTD.

The manufacturing processes and process parameters applied at Andover and BNT Mainz/Rentschler are slightly different, so are described separately in this report.

3.2.S.2.2 Description of manufacturing process and process controls

s 9(2)(b)(ii)



Module 3.2.P. Drug Product

3.2.P.1. Description and composition of the drug product

The drug product is a preservative-free white to off-white frozen sterile dispersion of RNA-containing lipid nanoparticles (LNPs) in aqueous cryoprotectant buffer (phosphate buffered saline and 300 mM sucrose at pH 7.4). The drug product is presented as a multi-dose concentrate in a clear glass 2 mL clear vial (type I glass), sealed with a synthetic bromobutyl rubber stopper, aluminium overseal and plastic flip-off cap. Each vial contains 0.45 mL of drug product and is designed to contain a total of 6 doses ~~5 doses~~ of 30 µg of RNA in 0.3 mL after thawing and dilution with 1.8 mL of sterile 0.9% sodium chloride injection (total volume of 2.25 mL). The drug product is administered by intramuscular injection.

A copy of the full formulation and quality standards applied to the excipients as detailed in the dossier is shown in Table 54. The formulation details as recorded in Medsafe's SMARTI database are also included in the attached Therapeutic Product Database Report.

Table 54: Formulation details of BNT162b2 drug product
Updated in roll 3

Name of Ingredients	s 9(2)(b)(ii)
BNT162b2 drug substance	
ALC-0315	
ALC-0159	
DSPC	
Cholesterol	
Sucrose	
Sodium chloride	
Potassium chloride	
Dibasic sodium phosphate, dihydrate[b]	
Monobasic potassium phosphate[c]	
Water for Injection	
Processing Aids/Resi	
Ethanol	
Citric acid monohydrate	
Sodium citrate	
Sodium hydroxide	
HEPES	
EDTA	

a. Values are rounded to maximum [illegible] trailing zeros not shown, where applicable. s 9(2)(b)(ii)
b. Dibasic sodium phosphate, dihydrate is named as disodium phosphate dihydrate in the Ph. Eur.
c. Monobasic potassium phosphate is named as potassium dihydrogen phosphate in the Ph. Eur.
d. The processing aids and drug substance formulation buffer components are residues that are essentially removed through the manufacturing process are not considered ingredients (excipients).
Abbreviations:
ALC-0315 = ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate)
ALC-0159 = 2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide
DSPC = 1,2-distearoyl-sn-glycero-3-phosphocholine
q.s. = quantum satis (as much as may suffice)
HEPES = 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid
EDTA = edetate disodium dihydrate

3.2.P.2. Pharmaceutical development

The pharmaceutical development of BNT162b2 utilised principles described in ICH Q8, risk assessments, development studies and prior experience with similar RNA-lipid nanoparticle vaccines.

3.2.P.2.1. Components of the drug product

3.2.P.2.1.1. Drug substance

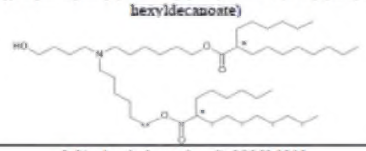
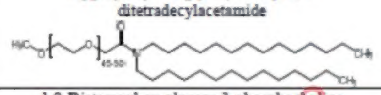
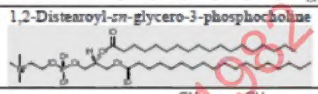
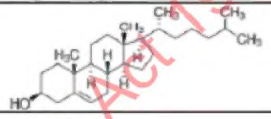
The drug substance (RNA) is provided for drug product manufacture as a frozen (-20 ± 5°C) aqueous solution (2.25 ± 0.25 mg/mL) in 10 mM 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (HEPES), 0.1 mM edetate disodium dihydrate (EDTA) at pH 7.0.

There are no obvious compatibility issues between the drug substance and the excipients present in the drug product formulation.

3.2.P.2.1.2. Excipients

The drug product contains RNA LNPs formulated in a phosphate-buffered saline (chosen for its ability to provide adequate buffering capacity at physiological pH), and 300 mM (103 mg/mL) sucrose (chosen as a cryoprotectant for frozen storage) at target pH 7.4. The drug product also contains four lipids that play a functional or structural purpose in the assembly and/or enable stabilisation of the RNA LNP. DSPC and cholesterol are structural lipids, providing a stable bilayer and enabling mobility of the lipid components within the LNP structure. ALC-0315 is an ionisable cationic lipid that is critical for successful delivery of RNA, ensuring the self-assembly of the LNP, the uptake of the LNP into the cells, and the escape of the RNA from the endosome. ALC-0159 is a PEGylated lipid that inserts itself in the outer lipid bilayer of the LNP, thereby providing a steric barrier to interactions with surfaces or other LNP that could result in particle fusion during storage. The structures of the lipid components are shown below. The nonclinical and clinical safety data for drug product containing these lipids is reviewed in separate Medsafe reports.

Table 55: Lipid components of the drug product

Lipid	Concentration (mg/mL)	Molecular Weight [Da]	Molecular Formula	Chemical Name (Synonyms) and Structure
ALC-0315[a]	7.17	766	$C_{48}H_{95}NO_5$	((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate) 
ALC-0159[b]	0.89	~2400-2600	$(C_2H_4O)_nC_{31}H_{63}NO_2$ n=45-50	2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide 
DSPC[c]	1.56	790	$C_{44}H_{88}NO_8P$	1,2-Distearoyl-*sn*-glycero-3-phosphocholine 
Cholesterol[d]	3.1	387	$C_{27}H_{46}O$	

a. CAS Number 2036272-55-4
b. CAS Number 1849616-42-7
c. CAS Number 816-94-4
d. CAS Number 57-88-5
Asterisks (*) indicate chiral centers for ALC-0315

s 9(2)(b)(ii)

s 9(2)(b)(ii)

Attachments

1. Therapeutic Product Database Report
2. Quality Evaluation Report Attachments
3. Novel Excipients Evaluation Report
4. Non-Clinical Evaluation Report
5. Clinical Evaluation Report

References

Collier, D.A., Meng, B., Ferreira, I.A.T.M, et al. Impact of SARS-CoV-2 B.1.1.7 Spike variant on neutralisation potency of sera from individuals vaccinated with Pfizer vaccine BNT162b2. medRxiv preprint doi: https://doi.org/10.1101/2021.01.19.21249840 (2021).

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Xie X, Zou J, Fontes-Garfias C et al. Neutralization of N501Y mutant SARS-CoV-2 by BNT162b2 vaccine-elicited sera. bioRxiv preprint https://doi.org/10.1101/2021.01.07.425740

Final Recommendation

A number of quality issues, and some clinical issues arising from this application still remain unresolved. The applicant has committed to providing the outstanding information to address these issues, with many of these issues aligning with the EMA/CHMPs specific obligations that were listed in the EU's conditional approval. Due to this outstanding information the product cannot be recommended for consent under Section 20 of the Medicines Act 1981 for distribution in New Zealand. However, due to the COVID-19 global pandemic situation and the clinical need for the product, provisional consent under Section 23 of the Medicines Act 1981 may be considered for the following indication:

COMIRNATY is indicated for active immunisation to prevent coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2, in individuals 16 years of age and older.

The use of this vaccine should be in accordance with official recommendations.

It is proposed that any provisional consent include the following conditions:

Provisional consent is to be granted for a period of nine months to address an urgent clinical need.

Provisional consent may only be renewed if the sponsor fulfils the following obligations within specified timelines, the dates of which may be altered on mutual agreement between Medsafe and the sponsor:

1) Prepare a Dear Healthcare Professional letter or comparable instructive material and provide this to Medsafe for review and approval prior to distribution of this product. Due date: February 2021.

2) The New Zealand site of batch release will only release batches for distribution in New Zealand once the importer or sponsor has verified that the shipping temperature profile meets specifications.

3) Provide Certificates of Analysis to Medsafe for the first three batches of vaccine intended to be distributed in New Zealand.

4) Provide data to further characterise the truncated and modified mRNA species present in the finished product. Data are expected to cover batches used in clinical trials (for which the characterisation data could be available earlier) and the PPQ batches. These data should address results from ion pairing RP-HPLC addressing 5'cap levels and presence of the poly(A) tail. These data should also address the potential for translation into truncated S1S2 proteins/peptides or other proteins/peptides. Relevant protein/peptide characterisation data for predominant species should be provided. Any homology between translated proteins (other than the intended spike protein) and human proteins that may, due to molecular mimicry, potentially cause an autoimmune process should be evaluated. Due date: July 2021, Interim report: March 2021.

5) Provide the analysis of the main peak of the RNA integrity test representing the full-length RNA, that addresses 5'cap levels and presence of the poly (A) tail. Due date: July 2021, Interim report: March 2021.

6) Provide the reassessment of the active substance specification for the DNA template purity and impurities. Due date: July 2021.